

Panel Discussion: Role of High Risk Groups in the Derivation of Environmental Health Standards

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We have heard a great many points reiterated, and I've tried to figure out some ideas that might have been missed. One thing is that some of us will go back into environments where standards for environmental contaminants are set. We must try to be cautious and not forget how ignorant we are.

We have heard the description of a variety of syndromes which lead to hypersusceptibility. These include groups which are especially exposed to high levels of chemicals; groups which are deficient in nutrients; and groups which are genetically predisposed to environmental chemical sensitivities. Thus we have the feeling that we know more—and we probably do—than most of our colleagues back home about hypersusceptibility. I think it is very important for us to remember though that there are enormous numbers of diseases of unknown etiology which may well have at least some etiological basis in environmental chemicals. There is increasing evidence that not only cancer but heart disease and many of the autoimmune diseases like rheumatoid arthritis, ulcerative colitis, regional enteritis, as well as respiratory diseases and even behavioral disorders and serious mental disorders, may be related in part to environmental chemicals. Even with the knowledge that we may have of hypersusceptible groups, I think that you should keep in mind Dr. Barth's opening remarks. We may still not yet know the major causes of environmental diseases. We may not have identified those most susceptible to environmental chemicals, either because they have illnesses which are caused by ubiquitous environmental chemicals or because we fail to realize that specific pre-existing diseases have made certain individuals more susceptible to environmental chemi-

cals. This means, of course, that the old-fashioned safety factor in setting standards may not be obsolete.

In recent years, particularly in the area of carcinogenesis we've been attempting at EPA to follow an interim policy which attempts to estimate the risk of the carcinogens to human populations so that these risk estimates can be used in risk benefit analyses. Open use of such analyses for setting environmental standards represents a relatively new development, as are congressional mandates to carry them out. I think probably, to some extent or another, risk-benefit analyses always have taken place in the setting of environmental standards, even though the language that was used to describe to the public what was taking place was that the levels that were being promulgated represented "safe" levels. This may not be dishonest. Paul Kotin mentioned this morning that safety does not necessarily mean absolute safety. When the Clean Air Act Amendments of 1970 were passed, there was a rather specific Congressional mandate to set the standards to protect the public health with a margin of safety, and the Congressional reports of the time reiterated that the margin of safety should protect high risk groups such as those with respiratory and chronic diseases. Certainly a review of the criteria used for EPA's 1971 Ambient Air Quality Standards, as well as recent reviews of research being considered when rewriting the Air Quality Criteria Documents, reveals that a great deal of emphasis has been given to studying high risk groups as well as the general population. These high risk groups have varied with the study of angina patients and persons with cardiac disabilities in the case of criteria for carbon monoxide to the arousal of respiratory symptoms in populations of asthmatics, chronic bronchitics, aged persons or infants in the case of nitrogen oxides, oxidants, sulfates, and

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sulfur oxides and particulates.

Since the Clean Air Act Amendments of 1970, some new features have been introduced into laws. For example, 1972 amendments to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), and the Toxic Substances Control Act of 1976 (TSCA), both use language that requires EPA to carry out risk-benefit analyses. These laws for the most part did not address standards by using the word "safety." Rather, concepts of risk were cited. To describe the risk of chemicals to a population, one would obviously have to understand the effect on hypersusceptibles as well. So these laws lead to involvement of the political process: the decision of weighing the risks, which health personnel would be instrumental in formulating, with the benefits which presumably would be formulated more by economists and politicians. In fact, this isn't entirely so. We as environmental health scientists are certainly aware of the work from the Johns Hopkins School of Public Health in the last few years showing the high incidence of suicide, depression, and cardiovascular disease related to unemployment. So we can appreciate that the trade-offs are not all between health and economics, but there are health components that are intimately related to the economic factors. A study of hypersusceptible groups by our environmental agencies need not be a "cop out" in terms of seeking to find ways of excluding such groups from protection. Rather, it is an awareness of the adverse effects of chemicals on hypersusceptible groups which permits us to consider such groups in the standard setting process. Earlier I urged that safety factors probably were still necessary because we might be only at the infancy of understanding the total effects of chemicals on human health. Nevertheless, we have to continue to increase our data base in order to be sure that our criteria are more accurate.

Another area of controversy that has come up has to do with the responsibility of the physician and environmental health scientist, whether he works for the government or for industry to take a stand for health. With the division of labor related to cost-benefit analysis in the derivation of environmental standards under TSCA and FIFRA, it might be thought that the physician's role has ended when he has defined the health risk, and that he can then step aside and let the lawyer-administrator and other decision makers decide how to weigh these risks and benefits. But I think it is again clear to us, because we recognize our own ignorance, that we must help our administrators, who are generally not

environmental health scientists but politicians and management specialists. We must help these individuals to understand our lack of knowledge. Increasingly, we're having to make decisions about chemicals that may have long-term adverse affects on the basis of a limited amount of animal data, largely because prudence dictates that we not expose individuals to animal carcinogens for several decades in order to find out whether or not they may turn out to be human carcinogens. Often we are dealing with just a few studies, even though they may be consistent, and a safety factor may be necessary because of lack of information available at the time when a decision appears prudent. Yet it is the duty of the environmental health scientists to provide to the decision maker with the best interpretation possible from such limited data.

The final point is: in setting standards for environmental contaminants, we must be aware that high risk groups are not a small portion of the population. We've often traditionally set standards by using safety factors of 100 below the no-effect levels of a pesticide which was given to a group of 50 mice; a food tolerance might be derived based on a safety factor of 100 below the no-effect level on such a feeding study. A factor of 100 may well be too small. We must remember that all embryos, fetuses, and neonates up to the age of about two or three months have immature enzyme detoxification systems; that infants and children don't reach mature levels of immunoglobulin A until they reach the ages of 10 to 12; that as we age, our immune system becomes less functional, making us more sensitive to carcinogens and respiratory irritants; that infants may be more susceptible because of increased absorption of pollutants as a function of their age; that retention of pollutants such as fluoride might be more common in individuals over the age of 50; that there are, after all, enormous numbers of pregnant women in our population who are more sensitive to chlorinated hydrocarbon insecticides, lead, and carbon monoxide; that every one of us have our susceptible times during the day because of circadian rhythms; and we've heard of course a lot about other factors, nutritional and genetic. Hypersusceptible groups are consequently not rare phenomena but include virtually everyone in the population from time to time.

Stanton Coerr*

In my view, we are already using information about high risk populations in formulating environmental regulations. I would like to talk about some of the issues that confront us in dealing with high risk groups.

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What we at EPA Office of Air Quality Planning and Standards try to do is match the scientific data base provided to us by the scientific community with what is required of us as an Agency by the laws under which we are operating. My specific experience is in drafting a proposed national air quality standard for lead. I am now working on the short-term NO₂ standard.

We are coming under increasing pressure to approach air standards in a consistent fashion—in other words, that the societal risk for high-risk groups exposed to ozone, NO₂, or lead be treated in comparable terms. I think this is good in some ways and not so good in other ways. There are situations in which you wish to keep specific flexibility to deal with what is unique to each pollutant, and other cases in which you wish to borrow some of the accepted approach of another standard.

Another problem we face is how many tiers of subgroups we consider in attempting to come up with a numerical level for a standard before we throw ourselves into margin of safety judgments. In the case of the lead standard, there were a number of candidate groups, principally small children and pregnant women, which for a variety of reasons could be regarded as sensitive. In addition to general sensitivity, certain children could also be seen as having genetic deficiencies, a deficient diet situation, or an exposure situation which would place them into a more sensitive subgroup than the general population. In the NO₂ short-term standard, most of the chamber work has been on adult volunteers, either bronchitic or normal, and we are aware of the fact that there might be more sensitivity in elderly or younger individuals, but we have no experimental data. Our general rule of thumb on this is that as long as we deal with groups in the general population of some significant size, we will determine the numerical thresholds for effects down to the point at which we no longer have data. After that point, we are left with qualitative estimation that there may be more effects for a certain group. We then tend to use margin of safety.

There is more than one way to treat sensitive groups. For example in the lead standard. We are using small children, as the sensitive population; instead of trying to move down to a more sensitive subgroup (those in the center city or children who are nutritionally at more risk), because we have good numbers on the statistical distribution of blood lead for a population of children, we can do some statistical work in estimating the mean blood lead at which a certain number of children or a certain percentage of children are below a given threshold

level.

When we get into lead, which is a multi-media, multi-source pollutant, we get ourselves into all kinds of tangles in trying to define what we would regard as a sensitive population with regard to air exposure alone. For example, we could with a certain amount of affection or compassion regard people who distill their own whiskey in radiators as being a sensitive population because they are very much lead-exposed. It's not clear, though, that the air standard should attempt to address that particular group.

I am aware that as we move from the scientific data base into regulatory judgments that relate to choosing sensitive populations and the thresholds for adverse effects and acceptable risk, we move away from the scientific principles about what is scientifically valid, to the principles of the regulatory world which are more those of the lawyer. When you take scientists away from the data base in dealing with validity into the regulatory world where validity is established through debate, you will get different kinds of answers about sensitive populations. Scientists are not comfortable moving into regulatory debates and they prefer not to speculate about risk in quite the same way as regulators.

Herbert L. Needleman*

In the brief time allotted, I shall try to address only two points: (1) the definition of "adverse health effect" in the context of contemporary medical practice; (2) recent studies of my group at Harvard Medical School which support the assertion that the threshold for adverse health effects is at least an inverse function of the sensitivity of the methods brought to bear. I shall use low level lead exposure as the model.

Recently, the Center for Disease Control issued a revised health standard on preventing childhood lead poisoning. This set the limit for undue lead exposure at 20 µg/dl. CDC found evidence to support this limit in the finding by Dr. Piomelli and others that free erythrocyte protoporphyrin (FEP) begins to rise at blood lead levels somewhere below 30 µg/dl, perhaps as low as 15 µg/dl. The lead industry has taken the position that an elevated FEP is not an adverse health effect; it is purely a biochemical change. This position, in fact, is the center of the industry's stance in regard to the Air Lead Criteria Document.

As a practicing physician I find myself called upon to make diagnostic and therapeutic judgments on the basis of incomplete data with regularity. Physicians generally employ early biochemical

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changes as guides to these decisions. I should like to list three examples where medical judgements are made which always cost money and frequently entail risk or discomfort. These judgements are made on the basis of biochemical changes which are not in themselves the essential disease state.

If a patient has a Kaiser-Fleischer Ring in the iris or an abnormal serum copper and a family history of Wilson's Disease, a prudent physician will commit that patient to penicillamine therapy, probably for the rest of his life.

If a child is born to a mother with a history of Rh incompatibility, has a positive Coombs test and a bilirubin greater than 5 mg, an exchange transfusion would be performed.

A child whose tuberculin reaction has converted within the past year would be placed on antituberculous therapy, even though the skin reaction is simply a collection of the immune chemicals and is not in itself threatening to the child.

Not to respond to the above biochemical changes is to run the risk of malpractice. I am comfortable with an elevated FEP as an adverse health effect. I do not think it is the core of the Air Lead Standard, but is certainly a helpful index to action.

I should like to comment on the recent work of my own group on the subject of neuropsychologic outcome in children at low doses of lead. I do not think low dose is the right phrase: unidentified lead intoxication is probably more precise.

In Boston we have been examining the neuropsychologic performance of first and second graders considered asymptomatic for lead who differ with respect to the concentration of lead in their deciduous teeth. It seems quite clear that the high dentine lead group have a mean IQ about 6 points below that of the low lead group. I recently presented this datum at the Society for Pediatric Research and was approached by a professor of pharmacology who asked me if I considered a 6 point difference in IQ of enough importance to warrant spending a great deal of money. I was and remain startled by this question.

Let me review our study briefly. We collected shed deciduous teeth from 75% of all first and second graders in Somerville and Chelsea, Massachusetts, and analyzed them for lead. We then excluded from the first analysis any child with a history of lead intoxication, low birth weight, or head injury, and brought in to the neuropsychologic clinic under strict double blind conditions children in the highest and lowest 20th percentiles for dentine lead. We controlled for 20 nonlead variables such as socioeconomic status, parental IQ, and

health history. We found that of 37 outcomes measured, the high lead group showed significant deficits (well below $p = 0.05$) on 14 measures. This study has been completed, and we are persuaded that lead at low dose does produce adverse health effects.

If we were to set the lead standard low enough to protect 95% of the population, that would appear at first to be acceptable performance. However, there are 17 million children under six years of age in this country. Protecting 95% from hazardous lead exposure would allow 850,000 to be at risk for brain damage. That clearly is not acceptable for any society which wishes to be remembered as authentically concerned about the welfare of its children.

Roy Albert *

Let's begin on a note of confusion in talking about the regulation of environmental carcinogens. The confusion deals with the concept of hypersusceptibility and how this relates to normal responses to carcinogens, and how these concepts in turn bear on our regulatory policies and of the nature of low level responses to carcinogens. I might say that the regulation of environmental carcinogens is still in a state of flux, particularly what constitutes an appropriate level of control; in other words, how severe the control of environmental carcinogens should be. There has been an explosive growth in the concern about regulating environmental carcinogens because of the demonstrated importance of environmental factors and the lack of satisfactory treatment of cancer. The dominant conceptual feature of the regulatory landscape at the present time is the linear nonthreshold dose-response relationship. The first surfaced in the 1950's during the debate about the health hazards, particularly cancer hazards from atomic fall-out from weapons testing. Data on Japanese survivors of the atomic bombing on leukemia suggested the consistency of the dose-response relationship with the linear nonthreshold dose response pattern. The support for the existence of this sort of a response pattern comes from the fact that it holds for the mutagenic action of ionizing radiation and chemical carcinogens and that there is a strong relationship between mutagenicity and carcinogenicity. The essence of the nonthreshold relationship is that no matter how small the dose, there is always a finite excess cancer risk. There is no such thing as a safe dose of carcinogen. This was translated in the late 50's into the Delaney Clause of the Food and Drug Act, which bans any agents as a food additive which show carcinogenic effects.

With the growth in the concern for the control of

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environmental carcinogens, its become apparent that many agents cannot be banned: they are simply too important. And, as I mentioned, it is unclear what constitutes a satisfactory level of control. We know that there are hypersusceptible responders to carcinogens. One only has to look at the situation with skin cancer induced by sunlight. It is essentially not a problem of heavily pigmented people. There is a considerably greater susceptibility among individuals that have fair skin, freckled complexions, red hair, generally of Celtic origin. Then at the far extreme of the spectrum of susceptibility, are the diseased individuals (xeroderma pigmentosum) who have a defect in their ability to repair DNA. Hypersusceptibility to sunlight-induced skin cancer thus has two components. One relates to the effective dose, namely the relative lack of pigmentation, and the second involves a defect in the underlying process of repair. Here, the underlying concept of hypersusceptibility is that susceptibility is a continuum and hypersusceptibles are at one end of the spectrum. It should be possible to protect everyone if the dose is sufficiently low.

A linear nonthreshold dose-response pattern, however, can imply a different concept, namely the probabilistic notion of a single-hit process. Getting cancer at very low levels of exposure to a carcinogen is like getting hit by a meteor. There is no need to invoke hypersusceptibility; it is just a mistake in DNA repair, like having a glass of water slip out of your hand. So we have two competing points of view. One is the notion of a probabilistic occurrence of a mistake in DNA repair in contrast to the notion that there are innate biological factors which exaggerate the response to carcinogens. There are very

significant theoretical and practical consequences of these two points of view. One is that if you are talking hypersusceptibility, you are talking about deterministic concept where everybody is on a track toward getting cancer sooner or later. The speed at which you progress toward getting cancer is related to the level of exposure and your susceptibility. This notion conveys the idea that there is a threshold in time; therefore if exposure is sufficiently low enough for any given level of susceptibility, cancer will not develop before the end of the normal lifespan.

The probabilistic approach, which implies a chance mechanism, is different in the sense that the time pattern of cancer occurrence is built into the biological processes and that the level of exposure determines the probability of cancer at any given time. So there is no real shift in time occurrence and there is no such thing as the time threshold.

At the present time, we are appearing to be locked into the probabilistic linear nonthreshold dose response, although the evidence for it is still quite scanty. The consequences of it are that one seeks to control exposure to extraordinarily low levels; that is, lifetime excess risk of more than one chance in a hundred thousand or one chance in a million or even less than that is not tolerable. And so we have the interesting circumstance that a conceptual point of view about normal patterns of response has fixed us into a mode of controlling carcinogens which is extraordinarily strict by any standard, and probably stricter than what we generally conceive of as the level of exposure required to control the response of hypersusceptibles.

General Discussion

DR. SENKER (*New England Medical Center*): I'd like to ask what is considered the significance in determining ambient air quality standards of childhood exposures and the relation that childhood exposures may have later on, particularly on pulmonary functions. Where should this fit into the setting of standards, given the difficulty in experimental situations or in, even determining the effect?

DR. NEEDLEMAN: I don't advertise myself as having any particular competence in the area of pulmonary disease. I do think that the issue of ambient air quality standards with respect to child health is a vital one. With regard to brain development, the studies of my group done in Philadelphia showed that children who lived in good housing but adjacent to lead industry had dentine lead levels as high as those in the center of the lead belt of Philadelphia. Dust levels in the school attended by these children reached as high as 5000 ppm. The latent effects of early exposure on later disability, whether pulmonary or neurologic, are of great importance. I think we spend an enormous amount of

money on things like orthodonture and elocution lessons and ignore the development of our children's brains.

DR. CARL SHY: There are some British studies on cohorts of children that do suggest that the frequency of respiratory disease in childhood is a risk factor for the development of obstructive lung disease in adulthood. There is also the other association between air pollution exposure and increased frequency of acute respiratory disease in childhood. But we just don't have much in the way of longitudinal data to answer your question.

MARVIN KAUFKSTEIN (*Science for the People*): I'd like to address my question to anyone who may be involved in drafting regulatory legislation. I think a concern which, at least from my point of view, comes out of our experience with regard to radiation standards and is still being debated with regard to guidelines and regulations with respect to recombinant DNA is the question of local options, local controls versus federal preemption. I wonder if panelists would like to comment on that.

STANLEY COERR: We don't draft legislation. Our legislation is clear. We set national standards. That debate was done in the Congress and they'll keep debating it there, but, I've never gotten into that.